I. REMARKS

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 8-9 are requested to be cancelled. Amendments to claims 1 and 14 are proposed. Support for the proposed amendments can be found at least in original claims 8-9. After amending the claims as set forth above, claims 1-7 and 10-14 will be pending in this application.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. REJECTIONS UNDER 35 U.S.C. § 103

The examiner continues to reject the claims under 35 U.S.C. §103(a) as being upatentable over on Lee et al. in view of Blazquez et al., Chee et al. (A) (WO 95/11995) and Sutcliffe; and in further view of Osano et al.; and over Lee et al. in view of Blazquez et al., Chee et al. (A) (WO 95/11995) and Sutcliffe and in further view of Chee et al. (B) and Routier; and over Lee et al. in view of Blazquez et al., Chee et al. (A) (WO 95/11995) and Sutcliffe and in further view of Behrensdor. Applicants respectfully traverse the rejections.

The present methods and kits involve microarrays with capture probes utilizing the 44 triplets provided in table 1 and their mutant counterparts for the specific detection of the beta-lactamases TEM, ESBL and IRT phenotypes. In addition, the microarrays employ sequences of between 3 and 20 nucleotides around the triplet specific of the TEM enzyme, which are not random sequences but are derived from the TEM gene. These sequences are used to obtain the specific hybridization of the beta-lactamase gene as explained in the examples and as outlined in the description of the probe sequences given in table 2. The sequences specific for the TEM beta-lactamase of the capture molecules presented in figure 2 have a length from 18 to 27 nucleotides and include the given triplet in their sequence. Applicants assert that the cited art does not presage the invention as presently claimed.

Lee et al. teach the use of arrays in which hybridization is indicative for the presence of a beta-lactamase resistance gene. This document concerns determination of presence or absence of some genes coding for different enzymes accountable for the resistance to a beta-lactam antibiotic. Lee et al. use the complete or great parts of the respective beta-lactamase genes as capture probes. *See* Lee et al., p. 194, left col., second sentence ("each beta-lactamase gene was confirmed with electrophoresis after PCR, and used as a DNA probe on the chip"). The PCR conditions disclosed comprise denaturation, hybridization and elongation times of 1 minute, respectively (cf. Lee et al., table 2), which are indicative for the amplification of much longer fragments than those specified in the present invention. Accordingly, Lee el al. neither disclose a detection of mutations in one gene nor a "gene walking"-approach as presently described.

While resistance to beta-lactam springs from the presence of the gene coding for the enzyme, it is also strongly influenced by specific mutations affecting the resistance or the non-resistance to specific antibiotic families. By the determining the presence or absence of an enzyme as outlined in Lee et al., it is not possible to gain information about resistance on the different types of antibiotics. Beta-lactamase enzymes with amino acid substitution(s) are variably active on oxy-imino-beta-lactam substrates, such as aztreonam, cefotaxime, cefiazidime and ceftriaxone or are resistant to inhibition by agents such as clavunalate, sulbactam and tazobactam (cf. table in Bush and Jacoby, J. Antimicrobioal. Chemotherapy 39, 1-3, 1997, enclosed). The effect of some single mutations on the antibiotic hydrolysis also is described by Blasquez et al. (Antimicrobial. Agents Chemo. 39, 145-149, 1995).

The present invention provides a screening tool not only for the presence or absence of an enzyme but for the presence or absence of a particular mutation in the TEM gene which will influence enzyme activity and specificity. It will be understood that the detection of the mutation can not be performed on one site alone but covers as much as possible the range of mutations that will affect the enzyme properties and as such the resistance activity of the bacteria and in turn a possible medical treatment.

Furthermore, the secondary references, whose teachings were discussed in applicants prior response, fail to cure the defects of the primary reference.

No combination of the cited documents, therefore, presages evaluating a full spectrum of mutations in a single assay as presently claimed. Nor would one of ordinary skill in the art have combined the cited documents to reach the claimed invention with a reasonable expectation of success. The challenge of determining multiple possible mutations by array is that every part to be questioned has to be present in the amplified solution and they all have to be able to hybridize on their respective capture probes with discrimination between the wild and the mutated sequence to be large enough to be considered as positive or negative. The determination of a significant difference of hybridization of one nucleotide sequence on two capture probes differing by a single nucleotide resides is not trivial. Applicants have shown, however, that the present method permits a fast screening for antibiotic resistances and enables an immediate provision of a specially tailored antibiotic treatment with minimum delay, for example in less than one working day (e.g. page 15, par. 63). Such results enhance patient health while reducing costs. Applicants request, therefore, that the rejection be withdrawn.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16, 1.17 and 41.20, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 23 July 2007 By

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (617) 342-4039
Facsimile: (617) 342-4001

R. Brian McCaslin
Attorney for Applicant
Registration No. 48,571